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Resurgence of Clinical Malaria in Ethiopia and Its Link to *Anopheles stephensi* Invasion

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Abstract: The invasion of *Anopheles stephensi* into Africa poses a potential threat to malaria control and elimination on the continent. However, it is not clear if the recent malaria resurgence in Ethiopia has linked to the expansion of *An. stephensi*. We obtained the clinical malaria case reports and malaria intervention data from the Ethiopian Ministry of Health (MoH) for the period 2001–2022. We analyzed clinical malaria hotspots and investigated the potential role of *An. stephensi* in the 2022 malaria outbreaks. Clinical malaria cases in Ethiopia decreased by 80%, from 5.2 million cases in 2004 to 1.0 million cases in 2018; however, cases increased steadily to 2.6 million confirmed cases in 2022. *Plasmodium vivax* cases and proportion have increased significantly in the past 5 years. Clinical malaria hotspots are concentrated along the western Ethiopian border areas and have grown significantly from 2017 to 2022. Major malaria outbreaks in 2022/2023 were detected in multiple sites across Ethiopia, and *An. stephensi* was the predominant vector in some of these sites, however, it was absence from many of the outbreak sites. The causes of recent upsurge in malaria in Ethiopia may be multi-factorial and it is a subject of further investigation.

Keywords: clinical malaria; *Anopheles stephensi*; urban area; outbreak; hot spot; knowledge gap

1. Introduction

Malaria morbidity and mortality have decreased significantly in the past two decades due to the scale-up of interventions, but malaria remains the most serious tropical infectious disease globally [1]. Worldwide in 2022, there were an estimated 249 million malaria cases in 85 malaria endemic countries and areas, an increase of 5 million cases compared with 2021, deaths declined in 2022 to 608,000 from 631,000 in 2020 [1]. In Ethiopia, malaria transmission has been a significant cause of public health issues due to its pronounced seasonal and regional fluctuation. Ethiopia is one of the few countries in Africa where *Plasmodium falciparum* and *Plasmodium vivax* are both endemic [2], making the malaria control and elimination more complex than the other malaria endemic African countries. Reported malaria cases decreased from a peak of 5.2 million in 2004 to 1.0 million in 2018 in Ethioia [1,2]. Encouraged by the progress made since 2000, Ethiopia envisaged the elimination of malaria and began a subnational program in 2017 and expanded to the national level in 2021, setting the goal of zero indigenous malaria cases by 2030 [3]. Despite these major achievements, there has been

an upsurge in malaria burden in Ethiopia in the past few years. The Ethiopian Ministry of Health (MoH) has confirmed 2.6 million malaria cases in 2022. In addition, the invasion of *Anopheles stephensi* Liston 1901 (Diptera: Culicidae), a malaria vector from South Asia, into Africa–with Ethiopia as the epicenter–and its rapid expansion in its new territory pose a significant threat to malaria control and elimination on the continent [4–8]. Since it was reported from Djibouti in 2012, *An. stephensi* has been detected in Ethiopia, Eritrea, Sudan, Somalia, Kenya, Nigeria, and Ghana [9]. The invasion of *An. stephensi* has been linked to malaria outbreaks in the urban areas of Djibouti and Ethiopia [10–13]. The World Health Organization (WHO) has called for urgent action to halt the spread of *An. stephensi* in Africa [9]. The Ethiopian MoH has updated its vector control policy in response to the new threat. To contain the spread of *An. stephensi*, the Ethiopian MoH partnered with The President's Malaria Initiative (PMI) launched a larval source management (LSM) program using microbial larvicide for *An. stephensi* control in eight cities in northeastern and central Ethiopia [14]. However, major knowledge gaps on *An. stephensi* ecology, behavior and its containment exist which may hamper vector control planning.

The aim of this study was to summarize the major achievements, challenges, and knowledge gaps in malaria control in Ethiopia from 2001 to 2022, to assess the changes in malaria epidemiology from 2017 to 2022, to document the new challenges in malaria control due to the invasion of *An. stephensi*, and to discuss the prospects for its control. The findings will be useful for guiding policy updates to contain the spread of *An. stephensi* and to minimize its impact on malaria transmission in Africa and specifically in Ethiopia, the current epicenter of the invasion.

2. Materials and Methods

We obtained the clinical malaria case reports, microscopy examination and rapid diagnostic test (RDT) results, antimalarial drug treatment records, insecticide-treated and long-lasting insecticidal net (ITN/LLIN) distribution records, and indoor residual spraying (IRS) coverage data from the Ethiopian MoH for the period 2001–2023. The nationwide clinical case reports included weekly microscopy and/or RDT confirmed cases, probable cases (clinically diagnosed), and parasite species at each woreda (administrative unit equivalent to district or county). Clinically reported cases were all symptomatic cases including both in-patients and out-patients. Probable cases were clinically diagnosed based on clinical symptoms but not confirmed by RDT or microscope. Microscopy and/or RDT results included the number of tested cases, positive cases, and parasite species, and these are all symptomatic cases. The malaria case data was provided by the MoH through the National Malaria Dashboard. Malaria treatment drugs delivered included artemisinin combination therapies (ACTs) and others. ITN/LLIN records included the number of nets distributed, and IRS data included population coverage.

We obtained the updated *An. stephensi* records, including *An. stephensi* distribution and year of detection, from the MoH, PMI, our field work (10 sites), and other published work (Figure 1) [4–6,15–18]. The proportion of *An. stephensi* included adults from reared larvae and from adult surveys. The MoH/PMI surveys used combined pyrethrum spray catches, CDC light trap, black box, animal baited net trap, clay pot, and Prokopack methods for mosquito adult samplings. About 150 house/nights were sampled at each site each month and collections were done for 6–9 months including both rainy and dry seasons. Our field surveillances were conducted at 6–9 villages/clusters at each site. We randomly selected 20 houses at each village/cluster for mosquito adult samplings using CDC light trap, BG-pro trap, and Prokopack methods. The samplings were conducted for 6–12 months including both rainy and dry seasons. Mosquito species were morphologically identified. The proportion of *An. stephensi* at each site was calculated as the number of *An. stephensi* adults divided by the total *Anopheles* adults captured. All study sites included 1-6 urban clusters and >3 rural villages. Surveys were conducted from 2017 to June 2023.
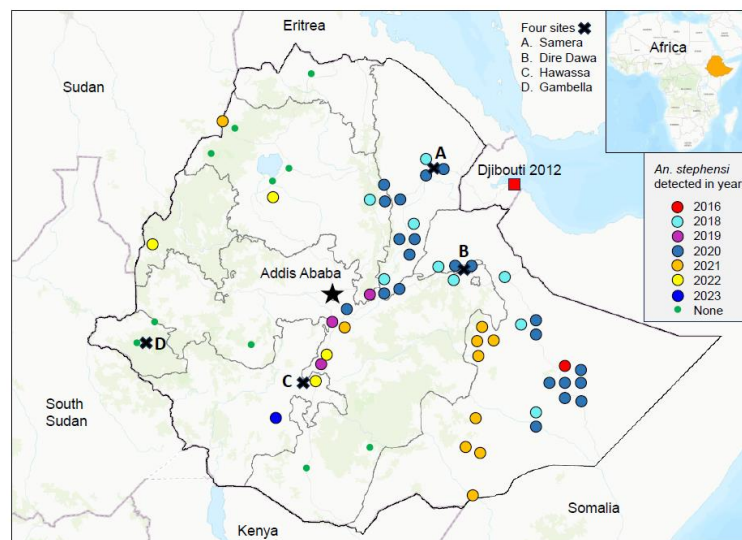
Figure 1. Distribution map of *An. stephensi* from 2016 to 2023 and the locations of the four study sites (shown in Figure 4) in Ethiopia.

To assess disease hotspots and their changes from 2017 to 2022, we analyzed woreda-level malaria incidence rates (cases/1000 persons at risk/year) based on the weekly outpatient records and population projections from the Ethiopia office of the United Nations Office for the Coordination of Humanitarian Affairs (https://data.humdata.org/organization/ocha-ethiopia accessed on 15 July 2023). We selected the period 2017–2022 for three reasons. Firstly, the changes in malaria incidence distribution and malaria management policy in Ethiopia from 2013 to 2016 have been studied [2]. Secondly and more importantly, *An. stephensi* was first detected in Kebri Dehar in the Somali Regional State in eastern Ethiopia in 2016, and 2017 could be seen as a key turning point for urban malaria in Ethiopia, as *An. stephensi* was detected in 9 other sites across eastern Ethiopia in 2018 (Figure 1) [5]. Thirdly, the latest complete clinical malaria cases data set we have obtained from the Ethiopian MoH was 2022 data. We determined hotspots and coldspots of clinical cases in 2017 and 2022 using the Optimized Hot Spot Analysis tool of ArcGIS 10.8.2 (ESRI, Redlands, CA 92373, USA), which calculates Getis-Ord Gi* spatial statistics and z-scores at significance levels of 90%, 95%, and 99% [19,20]. We analyzed malaria risk level changes from 2017 to 2022 based on the Ethiopian MoH risk classifications using annual parasite incidence (API), i.e., malaria free API = 0, very low risk 0–5, low risk 5–10, moderate risk 10–50, and high risk ≥50 annual parasite infection rate per 1000 people.

To analyze clinical malaria outbreaks, we randomly selected 40 districts representing different regions of Ethiopia, with at least three sites for each administrative region. All districts included at least one urban area and many rural villages, however, urban population varied from 35,000 residents at Semera-Logiya to 490,300 residents at Dire Dawa. We obtained the monthly confirmed malaria cases for the 40 sites for the period 2013–2022, aiming to determine if there were any outbreaks before 2022. We used Cullen's method to detect malaria outbreak months at each site from 2018 to 2023 based on 2013–2017 case numbers adjusted for population growth [21]. After initial evaluation of data completeness, 33 sites were included in the data analysis (Supplement Figure S1). At each district, the analysis of variance (ANOVA) with repeated measure was used to compare monthly clinical malaria incidences between 2022/2023 and 2017–2021. Since we have status of *An. stephensi* occurrence (Yes/No) and clinical malaria outbreaks (Yes/No) at each district, we used the 2 × 2 contingence table analysis to examine if *An. stephensi* played any role in malaria outbreaks in 2022/2023. The Kappa agreement index (range from −1 to 1) was calculated to measure the association, a value of -1 indicates a complete negative agreement, 0 shows no agreement, and 1 means a complete positive agreement.

3. Results

3.1. Malaria Epidemiology, Diagnosis, Treatment, and Prevention in Ethiopia

Nationwide, reported clinical malaria cases (probable plus confirmed) remained unchanged from 2001 to 2013, although with great fluctuations, and most of the reported cases were probable cases (Figure 2A). This was followed by a significant decline from 2013 (2.65 million confirmed cases and 0.67 million clinical cases) to 2018 (0.96 million confirmed cases and 0.08 million clinical cases). However, clinical malaria cases have increased slowly but steadily since 2018, reaching 2.65 million cases (2.60 million confirmed cases and 0.05 million clinical cases) in 2022 (Figure 1A). The proportion of *P. falciparum* malaria cases was stable from 2001 to 2014 and increased from 2014 to 2018, while the proportion of *P. vivax* cases increased from 10.6% in 2018 to 28.4% in 2022 (Figure 2A), reflecting a 7-fold increase in vivax malaria cases from 2018 (0.10 million) to 2022 (0.73 million). At the same time, the number of microscopically and RDT examined blood samples was stable from 2013 to 2021 (average of 6.5 million per year) and increased significantly to 9.8 million in 2022 (Figure 2B). Distribution of antimalarial drugs fluctuated but remained relatively stable from 2006 to 2022 (Figure 2C). The number of ITNs/LLINs delivered fluctuated greatly, with the major mass distributions occurring in 2007, 2010, 2015, and 2019 (Figure 2D). The IRS coverage reduced from 28.37 million people in 2009 to 8.86 million people in 2022 (Figure 2D).
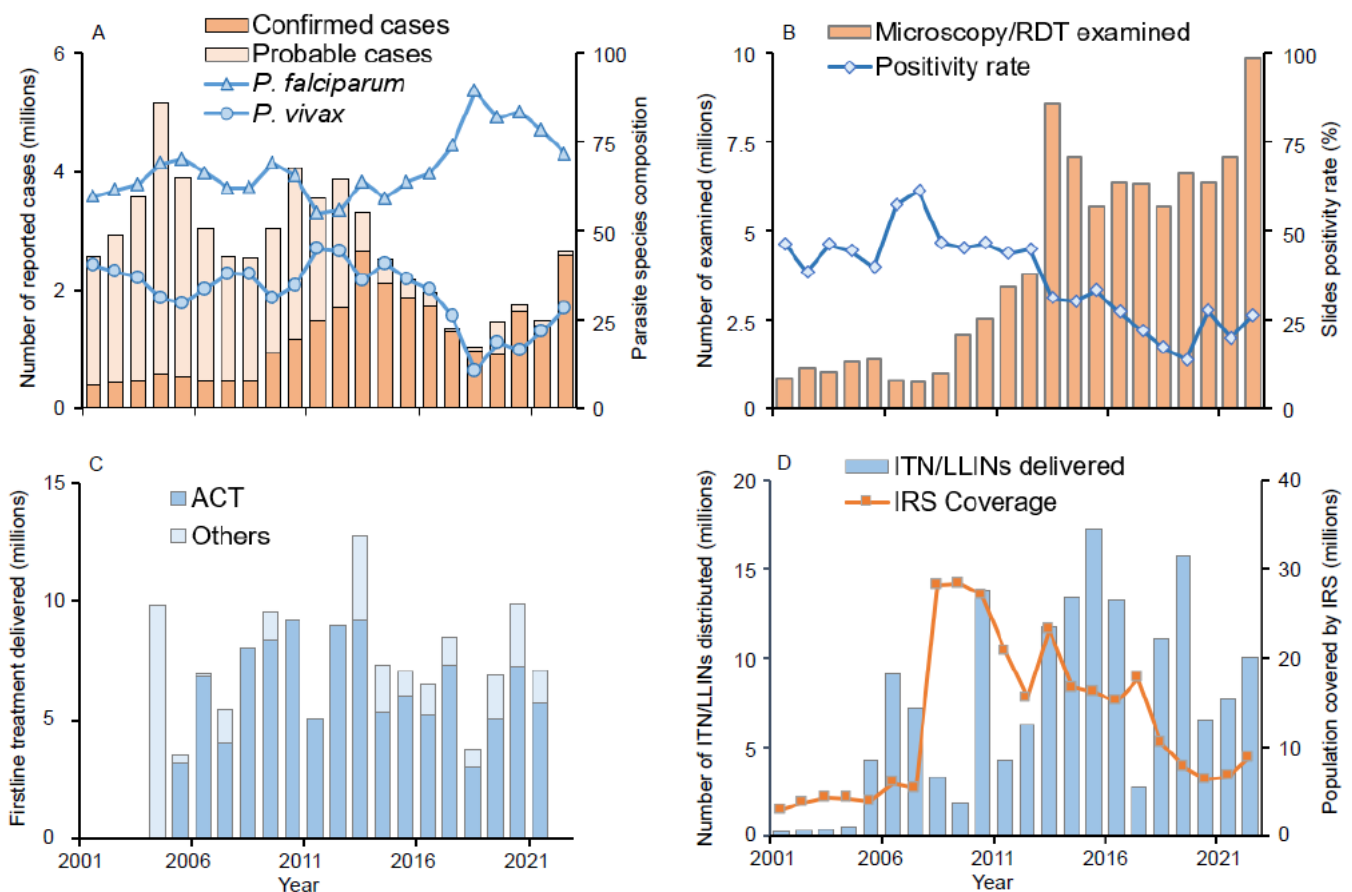

Figure 2. (**A**) Reported clinical malaria cases and parasite species composition from 2001 to 2022; (**B**) Number of RDT and microscopically examined blood samples and slide positivity rate from 2001 to 2022; (**C**) Antimalarial drugs delivered from 2005 to 2022; and (**D**) ITN/LLIN distribution and IRS population coverage from 2001 to 2022. ACT: Artemisinin–based combination therapy; ITN: Insecticide-treated nets; LLIN: Long-lasting insecticidal nets; IRS: Indoor residual spraying; RDT: Rapid diagnostic test.

3.2. Changes in Clinical Malaria Incidence from 2017 to 2022

Malaria risk levels increased significantly in many districts from 2017 to 2022, based on the changes in API (Table 1, Figure 3A,B, Supplement Table S1). For example, in 2017 there were 47 districts and 7.19 million people free of malaria (API = 0); by 2022, malaria-free areas had decreased to 19 districts and 2.42 million people (Table 1). The number of districts with high malaria risk increased from 161 districts (8.33 million people) in 2017 to 267 woredas (15.88 million people) in 2022 (Table 1). It is important to note that not all districts had an increased risk. For example, 32 districts where malaria risks were high in 2017 had decreased risk levels in 2022, while 205 districts with lower risk levels in 2017 jumped their risk levels in 2022 (Table 1, Figure 3A–C). Overall, from 2017 to 2022, malaria incidence rates decreased in 38 districts covering a population of 22,965,183 people, while malaria incidence rates increased in 780 woredas covering a population of 76,626,859 people. Malaria incidence remained unchanged (defined as change in malaria incidence rate < 0.1 cases/1000 people/year) in 38 woredas covering a population of 5,757,660 people.

Table 1. Changes in at-risk populations and number of woredas from 2017 to 2022.

| Risk Level ‡ | At Risk Woredas and Population † | | | | Risk Changes from 2017–2022 # | | | | | |
| | 2017 | | 2022 | | No Change | | Reduced | | Increased | |
	N Woreda	Population	N Woreda	Population	N Woreda	Population	N Woreda	Population	N Woreda	Population
API = 0	47	7,189,225	19	2,422,574	16	2,056,271	NA		31	5,132,954
API ≤ 5	478	58,200,085	339	43,763,043	270	36,176,014	3	366,303	205	21,657,768
5 < API < 10	148	13,092,751	129	13,451,299	30	2,884,527	25	2,028,818	93	8,179,406
10 ≤ API < 50	250	18,536,821	331	29,899,828	135	10,343,174	35	2,959,958	80	5,233,689
API ≥ 50	161	8,330,825	266	15,812,963	129	6,636,411	32	1,694,414	NA	
Total	1,084	105,349,707	1084	105,349,707	580	58,096,397	95	7,049,493	409	40,203,817

† Ethiopia population was estimated based on 2022 United Nations Office for the Coordination of Humanitarian Affairs. ‡ API values indicate the reduction/increase in API ranges. API: annual parasite incidence. # NA: not applicable. No change, reduced and increased represent risk levels (based on API categories) did not change, reduced and increased from 2017 to 2022, respectively, based on API observations in 2017 and 2022.
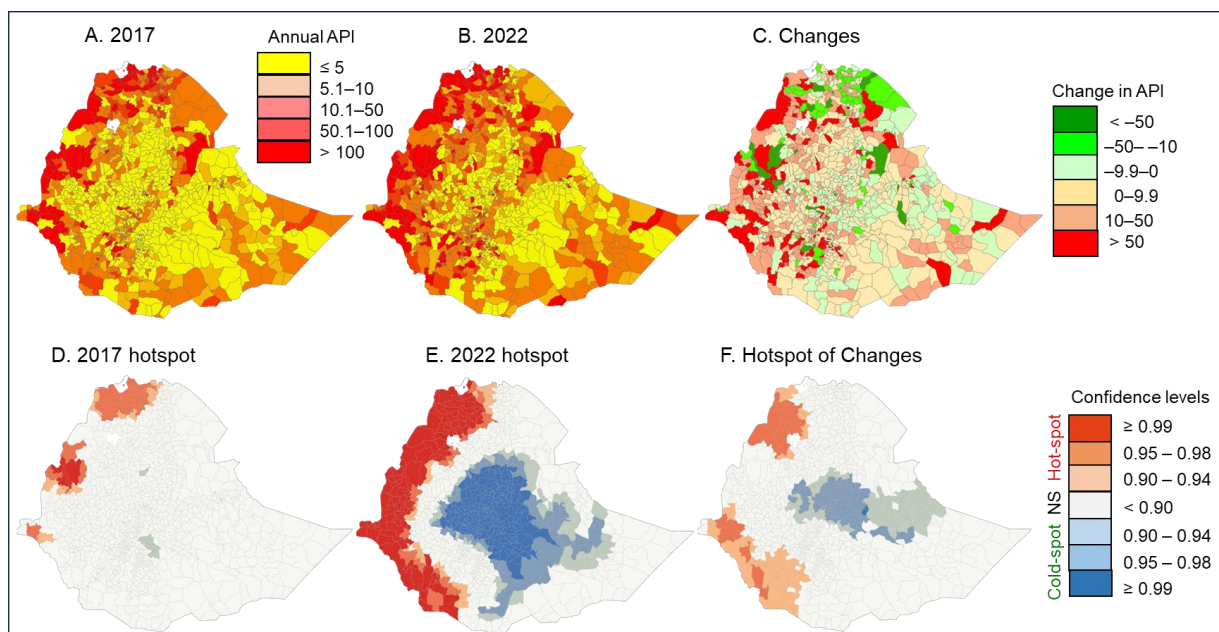

Figure 3. Top panel: Map of malaria annual parasite incidence (API) distribution in 2017 (**A**), 2022 (**B**), and changes from 2017 to 2022 (**C**). Bottom panel: The corresponding hot/cold spots detected from the API distribution; hotspotd for 2017 (**D**), 2022 (**E**) and changes in incidence (**F**).

Clinical malaria hotspots in 2017 were concentrated in three focal areas along the western Ethiopia borders, and no clear coldspots were detected (Figure 3D). By 2022, hotspot areas had expanded tremendously along the western borders and a large coldspot was detected in central Ethiopia (Figure 3E), revealing an increase in clinical malaria incidence in western Ethiopia. Hotspots of increase in clinical malaria occurred in northwestern and southwestern Ethiopia (Figure 3F).

3.3. Malaria Outbreaks and the Role of An. stephensi

Ten-year dynamics of clinical malaria showed a strong heterogeneity (Figure 4, Supplement Figures S2–S5). Figure 4 showed the examples of outbreaks detected from 2018 to 2023 in randomly selected four sites across Ethiopia, i.e., Semera, Dire Dawa, Hawassa and Gambella (Figure 1). In addition to outbreaks detected at all four sites in 2022/23, outbreaks were also detected in 2018 in Semera and Dire Dawa (Figure 4). So far *An. stephensi* has not been detected in Gambella despite 7 years of continuous field surveys (Figures 4 and S1). Trend of clinical malaria dynamics can be classified into four categories (Supplement Figures S2–S5), i.e., sudden recent outbreaks such as in Dire Dawa (Figure S2), declined trend with recent resurgence such as in Adama (Figure S3), stable trend with seasonality such as in Alamata (Figure S4), and overall declining trends such as in Abeshega and Yebelo (Figure S5). Malaria incidence rate increased significantly from 2017 to 2023 in many study sites, while it decreased significantly in other sites (Supplement Figures S2–S4). For example, clinical malaria incidence rates in Dire Dawa increased 9.0-fold in 2023 compared to the average of 2017–2021 (ANOVA with repeated measure, $p < 0.01$), while in Kemise Town it decreased about 40% during the same period ($p < 0.01$, Table 2). Overall, malaria outbreaks were detected in 25 of the 33 selected sites (Figure 4, Table 2, Supplement Figures S1–S5, Table S2), indicating the severity of malaria outbreaks in Ethiopia in 2022/23.
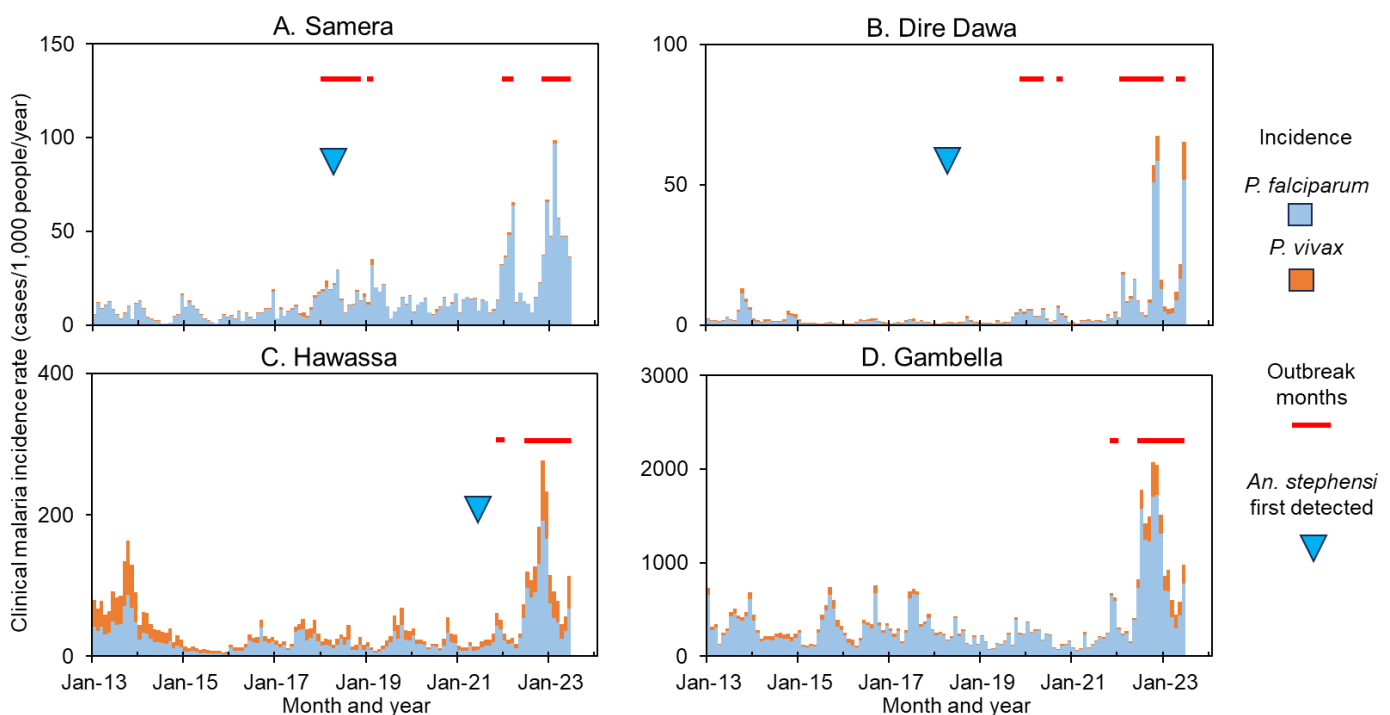

Figure 4. Example of dynamics and outbreaks detection in clinical malaria in selected study sites from 2013 to 2022. (**A**), (**B**), (**C**) and (**D**) respectively represent dynamics of clinical malaria trends in Samera, Dire Dawa, Hawassa, and Gambella.

Table 2. Malaria outbreak detection and *An. stephensi* status and proportion in study sites where mosquito samplings has been conducted.

Region	Woreada/City	Outbreak Detection			Anopheles Stephensi #	
		Status †	Rate Ratio ‡	*p*-Value §	Status	Proportion
Afar	Awash Fentale	No	0.87	0.0573	Yes	92%
	Semera	Yes	1.83	0.0334	Yes	100%
Amhara	Bahir Dar Town	Yes	2.69	0.0088	No	0%
	Debre Markos Town	Yes	2.46	0.0069	No	0%
	Gondar Zuriya	Yes	3.41	0.0007	No	0%
	Kemise Town	No	0.60	0.0036	No	0%
	Woreta	Yes	2.12	0.0297	No	0%
Benishangul-Gumuz	Assosa	Yes	1.47	0.0116	No	0%
	Bambasi	Yes	1.66	0.0013	No	0%
Dire Dawa	Dire Dawa	Yes	9.04	0.0093	Yes	96%
Gambella	Abobo	Yes	4.02	0.0020	No	0%
	Gambella	Yes	1.60	0.0112	No	0%
Oromia	Adama	Yes	1.64	0.1161	Yes	50%
	Batu	Yes	2.21	0.0328	Yes	77%
	Jimma Town	Yes	3.82	0.0030	No	0%
SNNP *	Arba Minch	Yes	1.18	0.1050	Yes	48.%
	Hawassa Town	Yes	3.01	0.0303	Yes	62%
Somali	Fik	No	0.69	0.0054	Yes	100%
	Godey	No	0.88	0.1020	Yes	64%
	Degehabur	Yes	1.01	0.4818	Yes	58%
	Kebri Dehar	Yes	1.52	0.0063	Yes	75%

† Outbreak status: Outbreak in 2022; ‡ Rate ratio: Incidence rate of 2022 over average of 2017–2021; § *p*-value indicating the significance of difference in clinical incidence between average of 2022 and average of 2017–2021; # Status of *An. stephensi*: based on data available until the end of 2023; Proportion of *An. stephensi*: Combination of larval-reared adults and adult collections. NA: Not available; SNNP * stands for Southern Nations, Nationalities and Peoples. Hawassa city is part of the Sidama Region which was a new region formed in 2020. For data analysis purpose, Hawassa city was considered as part of the old region.

The link between *An. stephensi* and malaria outbreaks was complex (Table 2, Supplement Table S2). The proportion of *An. stephensi* in some outbreak sites was high, for example, in Semera and Dire Dawa, *An. stephensi* accounted for 96–100% of all *Anopheles* adults collected in 2022, indicating a possible contribution of *An. stephensi* to the outbreaks (Table 2). Whereas, in Fik, no other *Anopheles* have been collected in 2022 except *An. stephensi*, there was a significant decrease in clinical malaria incidence in 2022 compared to 2017–2021 (Table 2). Furthermore, in many places where malaria outbreaks have been detected in 2022, for example, in Abobo and Gambella, no *An. stephensi* has been detected so far (Supplement Figures S1–S4, Table S2), i.e., outbreaks in some sites were independent of the existence of *An. stephensi*. The Kappa agreement index was −0.18, indicating no positive agreement between clinical malaria outbreaks and *An. stephensi* occurrence.

4. Discussion

Malaria morbidity and mortality have significantly decreased from early 2000 to 2018. Encouraged by the significant progress that has been achieved, the Ethiopian National Malaria Eradication Program (NMEP) has set the goal of achieving zero indigenous malaria in the country by 2030. However, the COVID-19 pandemic may have paused the declining trend in clinical malaria. The increase in clinical malaria since 2019 and the sudden malaria outbreak in Ethiopia in 2022–23 are alarming signs for malaria control. Clearly, *An. stephensi* is not the cause of the 2022 malaria outbreak in Ethiopia because malaria outbreak occurred in many places where *An. stephensi* has not been detected, however, malaria outbreaks in some urban areas might be associated with *An. stephensi*, because *An. stephensi* was nearly the sole malaria vector in some areas. The recent upsurge in clinical malaria in Ethiopia may be multi-factorial. Nonetheless, the outbreaks indicate the severity of the situation.

The WHO has reported a global increase in malaria cases in 2022; and Pakistan, Ethiopia and Nigeria were the three countries with increase of >1 million malaria cases from 2021 to 2022 [22]. The causes of the recent upsurge in clinical malaria in Ethiopia are worthy of in-depth investigations. Although its contribution is a subject of further investigation in Ethiopia, climate change might have major impact on malaria transmission and risk globally [23–25]. Civil unrest in northwestern Ethiopia caused the setting up of many internally displaced people's camps in the area, in addition, the influx of Sudanese refugees in southwestern Ethiopia (mainly in Gambella Region) led to the setup of refugee camps in the area, *Plasmodium* infections are prevalent in these camps and these infections may serve as reservoirs for local transmission [26–28]. More importantly, COVID-19 could have contributed to the malaria resurgence and outbreak by an accumulative effect [29–31]. COVID-19 pandemic interrupted not only the services at health facilities but also peoples' malaria treatment seeking behavior. Without effective treatment *Plasmodium* parasite reservoir might have cumulated from 2020 to 2021 and eventually caused the malaria outbreaks in Ethiopia in 2022, this hypothesis needs to be investigated. Although Ethiopian MoH has implemented the primaquine 14-day low-dose radical treatment of *P. vivax* since 2021, there was an increased proportion of clinical vivax malaria cases in 2022, the causes of such an increase requires further investigation. Other possible causes for the 2022 malaria outbreaks include but are not limited to the possible K13 gene mutation related antimalarial drug resistance by malaria parasite and potential missed diagnosis of P. falciparum infections due to the PfHRP2/3 deletions, both need further investigations. Lastly, we cannot rule out the contribution of *An. stephensi* in malaria outbreaks in Ethiopia because *An. stephensi* was the predominant in some urban areas in Ethiopia [11,12,15].

There are major knowledge gaps and policy implications to consider. The WHO recommends strengthening surveillance, including entomological surveillance, which can determine the spread of *An. stephensi* and its role in transmission, and malaria case surveillance, which can be used to investigate the impact of *An. stephensi* on malaria, particularly in urban areas. However, the optimal sampling method for *An. stephensi* adult mosquitoes has not yet been established. For example, aspiration (suction applied by a human or machine) is often used for *An. stephensi* adult samplings [15], but this method is highly subjective regarding the selection of sampling locations, i.e., one may intentionally select potential *An. stephensi* resting places such as animal shelters. Human landing catches (HLC) is considered the gold-standard for African *Anopheles* adult samplings [32–34], it will have similar problems; e.g., should one sit inside/outside human dwellings or inside/outside animal shelters? Similarly, for larval surveys one may deliberately select container habitats instead of randomly selecting both man-made and natural habitats. More importantly, these sampling methods may affect the population dynamics assessments [15,16]. Additionally, we must take into consideration of native African malaria and arboviral disease vectors, as they are present in some urban areas and may require different sampling methods than *An. stephensi*. Since we found most *An. stephensi* adults inside animal shelters, animal-baited traps may be an efficient trapping method, but it must be thoroughly evaluated under semi-field and field conditions. In any case, the sampling method(s) with less bias and better efficiency for both native African malaria vectors and *An. stephensi* need to be carefully investigated.

The WHO also recommends prioritizing research; specifically, it recommends evaluating the impact of vector control interventions, particularly new tools, against *An. stephensi* and focuses on research which will enable malaria control programs to find better ways to respond to this invasive vector. The Ethiopian government and PMI are conducting pilot larviciding programs using *Bacillus thuringiensis* var. *israelensis* (*Bti*) in a number of cities, aiming to generate data for strategic control of *An. stephensi*. This is a good starting point, as *An. stephensi* breeds mostly in man-made habitats such as artificial water containers and construction pits, however it is hard for LSM to cover all larval breeding habitats. Therefore, adult control tools should also be developed and evaluated. Since we know that *An. stephensi* rests mainly in animal shelters or other outdoor structures in

Ethiopia, we can develop new mosquito control methods utilizing this information [35]. For example, targeting animal shelters with IRS may significantly reduce the population density of *An. stephensi*. Regardless, integration of different control tools and including both larval and adult interventions may help to greatly reduce the *An. stephensi* population if not eliminate it.

There are limitations regarding the clinical malaria case reporting and the investigations of the causes of the 2022 malaria outbreaks in Ethiopia. In Ethiopia, private clinics also provide service for malaria diagnosis and treatment, however, compared to the free malaria treatment at government-run public healthcare facilities, the cost at private clinics may prevent some patients from seeking treatment over their facilities. Therefore, the under-report of clinical malaria cases from private clinics may not be a major issue. The causes of the 2022 malaria outbreaks in Ethiopia may be multi-factorial, which requires further investigations, and this can be a major study itself. Another limitation is the clinical malaria case dynamics at each woreda, it would be better to used incidence rate based on population size, however, because the Ethiopian government has not done any census since 2007 and some woredas have been redraw in the past 10 years, therefore it is very difficult to calculate incidence rate over time. When linking malaria outbreaks with *An. stephensi*, we have noted that mosquito larval and adult surveys to detect *An. stephensi* occurrence have been conducted at 61 sites across Ethiopia as of 2023. However, there are limitations on mosquito data, because the sampling schemes were not systematically designed. For example, some mosquito surveys were conducted only once while others were done multiple months at each site. Samplings also used different trapping methods. Nonetheless, standardized mosquito sampling strategy should be developed and implemented so that results can be generalized across different eco-epidemiological settings.

5. Conclusions

While the malaria burden in Ethiopia has been greatly reduced in the past 20 years, the 2022–2023 malaria outbreak has undercut control efforts. Although the overall contribution of *An. stephensi* to malaria transmission in Africa is unclear, it has been linked to the malaria outbreaks in some urban settings of Africa. Larviciding has been implemented in Ethiopia for controlling *An. stephensi*, but adult control strategies should also be developed. The rapid growth of many African cities and global climate change, coupled with the invasion and spread of this highly efficient and adaptable malaria vector and the knowledge gaps surrounding it, could undermine the malaria control and elimination efforts in Ethiopia and other African countries. Containing the spread of *An. stephensi* and eliminating malaria in Africa requires strong international collaboration, investment, and commitment.

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Abbreviations

ACT: artemisinin combination therapies; ANOVA: analysis of variance; API: annual parasite incidence; *Bti*: *Bacillus thuringiensis* var. *israelensis*; HLC: human landing catches; IRS: indoor residual spraying; ITN: insecticide-treated bed net; LLIN: long-lasting insecticidal net; LSM: larval source management; MoH: Ministry of Health; NMEP: National Malaria Eradication Program; PMI: the President's Malaria Initiative; RDT: rapid diagnostic test; WHO: World Health Organization.

References

1. World Health Organization. World Malaria Report 2023. 2023. Available online: https://www.who.int/publications/i/item/9789240086173 (accessed on 5 October 2023).
2. Taffese, H.S.; Hemming-Schroeder, E.; Koepfli, C.; Tesfaye, G.; Lee, M.-C.; Kazura, J.; Yan, G.-Y.; Zhou, G.-F. Malaria epidemiology and interventions in Ethiopia from 2001 to 2016. *Infect. Dis. Poverty* **2018**, *7*, 103. [CrossRef] [PubMed]
3. Ministry of Health, E. National Malaria Elimination Program. Addia Ababa: Minstry of Helth, Ethiopia. 2021. Available online: http://dataverse.nipn.ephi.gov.et/bitstream/handle/123456789/1526/Ethiopia-Malaria-Elimination-Strategic-Plan-2021-2025-Agust-31.pdf?sequence=1 (accessed on 5 September 2023).
4. Balkew, M.; Mumba, P.; Dengela, D.; Yohannes, G.; Getachew, D.; Yared, S.; Chibsa, S.; Murphy, M.; George, K.; Lopez, K.; et al. Geographical distribution of *Anopheles stephensi* in eastern Ethiopia. *Parasit. Vectors.* **2020**, *13*, 35. [CrossRef] [PubMed]
5. The PMI VectorLink. Ethiopia Project Final Entomology Report May 2019-March 2020. Rockville, MD: Abt Associates. 2020. Available online: https://pdf.usaid.gov/pdf_docs/PA00ZC3Z.pdf (accessed on 10 July 2023).
6. Balkew, M.; Mumba, P.; Yohannes, G.; Abiy, E.; Getachew, D.; Yared, S.; Worku, A.; Gebresilassie, A.; Tadesse, F.G.; Gadisa, F.; et al. An update on the distribution, bionomics, and insecticide susceptibility of *Anopheles stephensi* in Ethiopia, 2018-2020. *Malar. J.* **2021**, *20*, 263. [CrossRef]
7. Hamlet, A.; Dengela, D.; Tongren, J.E.; Tadesse, F.; Bousema, T.; Sinka, M.; Seyoum, A.; Irish, S.R.; Armistead, J.S.; Churcher, T. The potential impact of *Anopheles stephensi* establishment on the transmission of *Plasmodium falciparum* in Ethiopia and prospective control measures. *BMC Med.* **2022**, *20*, 135. [CrossRef]
8. Carter, T.E.; Yared, S.; Gebresilassie, A.; Bonnell, V.; Damodaran, L.; Lopez, K.; Ibrahim, M.; Mohammed, S.; Janies, D. First detection of *Anopheles stephensi* Liston, 1901 (Diptera: Culicidae) in Ethiopia using molecular and morphological approaches. *Acta. Tropica* **2018**, *188*, 180–186. [CrossRef]
9. World Health Organization. WHO Initiative to Stop the Spread of *Anopheles stephensi* in Africa. 2023. Available online: https://www.who.int/publications/i/item/WHO-UCN-GMP-2022.06 (accessed on 2 May 2024).
10. Emiru, T.; Getachew, D.; Murphy, M.; Sedda, L.; Ejigu, L.A.; Bulto, M.G.; Byrne, I.; Demisse, M.; Abdo, M.; Chali, W.; et al. Evidence for a role of *Anopheles stephensi* in the spread of drug- and diagnosis-resistant malaria in Africa. *Nat. Med.* **2023**, *29*, 3203–3211. [CrossRef]
11. Teka, H.; Golassa, L.; Medhin, G.; Balkew, M.; Sisay, C.; Gadisa, E.; Nekorchuk, D.M.; Wimberly, M.C.; Tadesse, F.G. Trend analysis of malaria in urban settings in Ethiopia from 2014 to 2019. *Malar. J.* **2023**, *22*, 235. [CrossRef]
12. de Santi, V.P.; Khaireh, B.A.; Chiniard, T.; Pradines, B.; Taudon, N.; Larréché, S.; Mohamed, A.B.; de Laval, F.; Berger, F.; Gala, F.; et al. Role of *Anopheles stephensi* Mosquitoes in Malaria Outbreak, Djibouti, 2019. *Emerg. Infect. Dis.* **2021**, *27*, 1697–1700. [CrossRef] [PubMed]
13. Zayed, A.; Moustafa, M.; Tageldin, R.; Harwood, J.F. Effects of seasonal conditions on abundance of malaria vector *Anopheles stephensi* mosquitoes, Djibouti, 2018–2021. *Emerg. Infect. Dis.* **2023**, *29*, 801–805. [CrossRef]
14. PMI. Ethiopia Malaria Operational Plan FY 2023. US President's Malaria Initiative. 2023. Available online: https://d1u4sg1s9ptc4z.cloudfront.net/uploads/2023/01/FY-2023-Ethiopia-MOP.pdf (accessed on 4 May 2024).

15. The PMI VectorLink Project. Ethiopia Final Entomological Report, April 2022-March 2023. Rockville, MD. Abt Associates Inc. 2023. Available online: https://d1u4sg1s9ptc4z.cloudfront.net/uploads/2023/09/Entomological-Monitoring-Report-Ethiopia-2023.pdf (accessed on 10 May 2024).

16. The PMI VectorLink Project Ethiopia. Ethiopia Final Entomological Report, APRIL 2021-MARCH 2022. In: PMI, editor. Rockville, MD: Abt Associates. 2022. Available online: https://d1u4sg1s9ptc4z.cloudfront.net/uploads/2023/02/Entomological-Monitoring-Report-Ethiopia-2022.pdf (accessed on 10 November 2023).

17. The PMI VectorLink Project Ethiopia. Ethiopia Final Entomology Report May 2020-March 2021. Rockville, MD, USA: The PMI VectorLink Project, Abt Associates Inc. 2021. Available online: https://pdf.usaid.gov/pdf_docs/PA00ZC42.pdf (accessed on 10 January 2024).

18. Teshome, A.; Erko, B.; Golassa, L.; Yohannes, G.; Irish, S.R.; Zohdy, S.; Dugassa, S. Laboratory-based efficacy evaluation of *Bacillus thuringiensis* var. *israelensis* and temephos larvicides against larvae of *Anopheles stephensi* in Ethiopia. *Malar. J.* **2023**, *22*, 48. [CrossRef]

19. Getis, A.; Ord, J.K. The analysis of spatial association by use of distance statistics. *Geogr. Anal.* 1992; 24, 189–206. [CrossRef]

20. Ord, J.K.; Getis, A. Local spatial autocorrelation statistics: Distributional issues and an application. *Geogr. Anal.* **1995**, *27*, 286–306. [CrossRef]

21. Cullen, J.R.; Chitprarop, U.; Doberstyn, E.B.; Sombatwattanangkul, K. An epidemiological early warning system for malaria control in northern Thailand. *Bull World Health Organ* **1984**, *62*, 107–114. Available online: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2536271/ (accessed on 10 June 2024). [PubMed]

22. World Health Organization. World Malaria Report 2023. 2023. Available online: https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2023 (accessed on 10 June 2024).

23. Li, C.; Managi, S. Global malaria infection risk from climate change. *Environ. Res.* **2022**, *214*, 114028. [CrossRef]

24. Lubinda, J.; Haque, U.; Bi, Y.; Hamainza, B.; Moore, A.J. Near-term climate change impacts on sub-national malaria transmission. *Sci. Rep.* **2021**, *11*, 751. [CrossRef]

25. Leal Filho, W.; May, J.; May, M.; Nagy, G.J. Climate change and malaria: Some recent trends of malaria incidence rates and average annual temperature in selected sub-Saharan African countries from 2000 to 2018. *Malar. J.* **2023**, *22*, 248. [CrossRef]

26. Ahmed, A.; Mulatu, K.; Elfu, B. Prevalence of malaria and associated factors among under-five children in Sherkole refugee camp, Benishangul-Gumuz region, Ethiopia. A cross-sectional study. *PLoS ONE* **2021**, *16*, e0246895. [CrossRef]

27. Asebe, G.; Mamo, G.; Wieland, B.; Medhin, G.; Tilahun, G.; Abegaz, W.E.; Legesse, M. Community awareness and experiences of health workers concerning mosquito-borne viral diseases in selected districts of Gambella Region, Southwestern Ethiopia. *Infect. Ecol. Epidemiol.* **2021**, *11*, 1988453. [CrossRef] [PubMed]

28. Allan, R.; Weetman, D.; Sauskojus, H.; Budge, S.; Hawail, T.B.; Baheshm, Y. Confirmation of the presence of *Anopheles stephensi* among internally displaced people's camps and host communities in Aden city, Yemen. *Malar. J.* **2023**, *22*, 1. [CrossRef]

29. Weiss, D.J.; Bertozzi-Villa, A.; Rumisha, S.F.; Amratia, P.; Arambepola, R.; Battle, K.E.; Cameron, E.; Chestnutt, E.; Gibson, H.S.; Harris, J.; et al. Indirect effects of the COVID-19 pandemic on malaria intervention coverage, morbidity, and mortality in Africa: A geospatial modelling analysis. *Lancet Infect. Dis.* **2021**, *21*, 59–69. [CrossRef]

30. Gao, L.; Shi, Q.; Liu, Z.; Li, Z.; Dong, X. Impact of the COVID-19 pandemic on malaria control in Africa: A preliminary analysis. *Trop. Med. Infect. Dis.* **2023**, *8*, 67. [CrossRef]

31. Mungmunpuntipantip, R.; Wiwanitkit, V. Malaria and COVID-19 in malarial endemic area: Incidence and coincidence. *Turkiye Parazitolojii Dergisi.* **2022**, *46*, 84–85. [CrossRef] [PubMed]

32. Sanou, A.; Moussa Guelbéogo, W.; Nelli, L.; Hyacinth Toé, K.; Zongo, S.; Ouédraogo, P.; Cissé, F.; Mirzai, N.; Matthiopoulos, J.; Sagnon, N. Evaluation of mosquito electrocuting traps as a safe alternative to the human landing catch for measuring human exposure to malaria vectors in Burkina Faso. *Malar. J.* **2019**, *18*, 386. [CrossRef] [PubMed]

33. Govella, N.J.; Maliti, D.F.; Mlwale, A.T.; Masallu, J.P.; Mirzai, N.; Johnson, P.C.; Ferguson, H.M.; Killeen, G. An improved mosquito electrocuting trap that safely reproduces epidemiologically relevant metrics of mosquito human-feeding behaviours as determined by human landing catch. *Malar. J.* **2016**, *15*, 465. [CrossRef]

34. Kenea, O.; Balkew, M.; Tekie, H.; Gebre-Michael, T.; Deressa, W.; Loha, E.; Lindtjørn, B.; Overgaard, H.J. Comparison of two adult mosquito sampling methods with human landing catches in south-central Ethiopia. *Malar. J.* **2017**, *16*, 30. [CrossRef] [PubMed]

35. Ahmed, A.; Abubakr, M.; Ali, Y.; Siddig, E.E.; Mohamed, N.S. Vector control strategy for *Anopheles stephensi* in Africa. *Lancet Microbe* **2022**, *3*, e403. [CrossRef]